Psychological Medicine, 2001, **31**, 1231–1236. © 2001 Cambridge University Press
DOI: 10.1017/S0033291701004603 Printed in the United Kingdom

The differential impact of age on the phenomenology of melancholia

G. PARKER,[1] K. ROY, D. HADZI-PAVLOVIC, K. WILHELM AND P. MITCHELL

From the School of Psychiatry, University of New South Wales; and the Mood Disorders Unit, Prince of Wales Hospital, Sydney, NSW, Australia

ABSTRACT

Background. We pursue an observation that age may influence the clinical features of melancholia and, in particular, psychomotor disturbance.

Methods. Two large clinical databases were amalgamated allowing the clinical features of 124 depressed subjects meeting DSM-III-R and clinical criteria for melancholia to be contrasted with 218 subjects diagnosed as having a non-melancholic depression by both criteria sets. Psychomotor disturbance was assessed by the CORE measure and by seven classical endogeneity symptoms of melancholia which, when summed, created a ENDOG score.

Results. There was no impact of age on ENDOG scores in either the melancholics or non-melancholics. In the melancholics, increasing age was associated with increasing CORE scores and with agitation scale scores in particular. In a set of discriminant function analyses seeking to identify the comparative utility of a set of predictors of melancholic (*versus* non-melancholic) groups, age was significant, and while CORE and ENDOG scores were individual predictors, their combined entry established that the CORE score alone made the ENDOG score redundant, and that the addition of age then made little impact.

Conclusions. Melancholia appears to have a later age of onset than non-melancholic depression, while its phenotypic expression appears to change with age, with psychomotor disturbance being more distinct in older subjects. Such an effect may have a number of clinical implications, including possible differential effects of varying antidepressant treatments.

INTRODUCTION

In a series of publications we have argued that differing pathophysiological processes are involved in melancholic and (residual) non-melancholic depression, and that observable psychomotor disturbance (PMD) is a key marker of melancholia. For differentiating the contrasting depressive 'types', PMD appears to be superior to the mood and vegetative endogeneity symptoms, which made up the classical criteria for 'endogenous depression' (Parker *et al*. 1990, 1994; Parker & Hadzi-Pavlovic, 1996). Furthermore, we have argued that PMD is both 'necessary' (in the sense that all those with true melancholia should evidence PMD) and largely 'sufficient' in that, if PMD is evident, it renders endogeneity symptoms almost redundant in distinguishing melancholic from non-melancholic depression (Parker *et al*. 1995).

The CORE measure was developed to assess PMD observationally. The refined measure (Parker *et al*. 1994) has a set of 18 items contributing to three scales ('non-interactiveness', 'retardation' and 'agitation') reflecting the cognitive and motoric components of PMD. In our two CORE development studies (Parker & Hadzi-Pavlovic, 1996), we established that CORE scores increased with age, which we interpreted as a reflection of the recognized phenomenon that melancholia is more likely to

[1] Address for correspondence: Professor Gordon Parker, Euroa Unit, Prince of Wales Hospital, Randwick, NSW 2031, Australia.

commence at an older age than non-melancholic depression. Subsequent clinical observation has suggested that, in people whom we judge cross-sectionally and longitudinally as highly likely to have 'melancholia', PMD is less severe in younger subjects (i.e. those less than 30 years), and particularly in those with a unipolar course. That clinical observation suggests the possibility of an age effect on the presentation of PMD, which could impact on the capacity of the CORE measure to assign subjects as having a melancholic or non-melancholic depression. Alternatively, age might have a general effect on the clinical presentation of melancholia, and thus influence endogeneity symptoms as well as PMD. Thus, in the present paper, we considered whether age influences both CORE scores and historically favoured endogeneity symptoms and if so, the implications for both the definition and pathogenesis of melancholia.

METHOD

Our analyses are undertaken on two consolidated samples, CORE-II (the sample where the CORE measure was refined) and PAL-I (our subsequent sample), and with each described elsewhere (Parker *et al*. 1994, 1998 respectively) in some detail. Sample members comprised depressed in-patients and out-patients referred to our tertiary referral Mood Disorders Unit (MDU), and those who tended to have more severe and treatment resistant disorders; as well as a less severe and chronic subsample of depressed patients who were routine referrals to our consultants. Medication details were not recorded in our database but most patients, when assessed, were receiving an antidepressant, some a mood stabilizer and only a small percentage were receiving a neuroleptic drug. All study subjects were required to meet DSM-III-R criteria for the presence of major depression for less than 2 years. Subjects completed self-report measures, and were then interviewed by research psychologists and psychiatrists who administered structured and open-ended assessment schedules.

We now detail data considered in this report. Our assessing MDU psychiatrists administered the 21-item Hamilton scale (Hamilton, 1967) as a measure of depression severity, quantified PMD by use of the CORE, rated whether the patient met lifetime criteria for bipolar disorder and generated 'clinical diagnoses'. The last comprised 'psychotic depression' (when there was clear evidence of delusions and/or hallucinations); melancholic/endogenous depression (when there was clear evidence of 'classical' endogeneity features such as vegetative symptoms, non-reactive mood, pervasive anhedonia and psychomotor disturbance); as well as two non-melancholic classes (i.e. neurotic and reactive depression) that respectively weight a personality contribution and a situational stressor as distinctly relevant. Depressive symptoms were assessed either by self-report or by clinical questions, with most scored on four-point scales (assessing absence (coded 0) of a feature *versus* its presence as mild (1), moderate (2) or severe (3), and with the psychiatrist required to judge whether the patient was at episode 'nadir' or not.

In this study, we focused on seven endogeneity symptoms (i.e. appetite and weight loss, anticipatory and consummatory anhedonia, mood worse in the morning, non-reactive mood and slowed physically) that represent all melancholic clinical feature criteria listed in DSM-III-R and all bar two problematic items for rating – distinct quality and excessive or inappropriate guilt – in DSM-IV. We examined such data principally to determine if there is any evidence of an age effect on endogeneity and CORE scores.

RESULTS

Overall sample characteristics

Our analyses are undertaken on the combined databases, after deleting all subjects who received a clinical diagnosis of psychotic depression and those who were judged not to be at depression nadir when clinically assessed, leaving a sample of 458 subjects. These sample members had a mean age of 43·6 (S.D. 15·9) years, a mean age at first episode of 30·7 (S.D. 16·8) years, a mean number of 7·9 (S.D. 16·5) lifetime episodes, and mean CORE and Hamilton scores of 5·3 (S.D. 5·4) and 21·3 (S.D. 7·3) respectively.

Defining melancholic and non-melancholic samples

We then created two subsamples of those with melancholic depression (or MEL) who met both: (*i*) our clinical diagnostic criteria for endogenous

https://doi.org/10.1017/S0033291701004603 Published online by Cambridge University Press

depression; and (*ii*) DSM-III-R criteria of major depression with melancholia ($N = 124$). They were to be compared with 218 non-melancholic depression (NON-MEL) subjects who did not meet: (*i*) melancholic clinical diagnostic criteria; and (*ii*) DSM melancholic criteria, while the remaining 116 subjects (who had been variably assigned by each system) were not considered in our analyses. The MEL and NON-MEL groups had mean ages of 54·6 (S.D. 16·9) and 36·2 (S.D. 11·7) years respectively, a significant difference ($t = 11·9$, $P < 0·001$) of 18 years. The MEL group also differed in reporting an older age at their first depressive episode (41·5 *v.* 23·8, $t = 10·6$, $P < 0·001$), again an 18-year difference. Summed endogeneity (i.e. ENDOG) scores were higher for the MEL than for the NON-MEL group (16·1 *v.* 10·4, $t = 11·0$, $P < 0·001$), while the Hamilton scores were comparable for the respective groups (22·2 *v.* 20·8, $t = 1·6$), with the latter suggesting that the MEL and NON-MEL had a similar level of depression severity. Total CORE scores were weakly associated with total ENDOG scores in both the MEL ($r = 0·29$, $P < 0·01$) and NON-MEL ($r = 0·26$, $P < 0·01$) subjects, suggesting some overlap.

Impact of age on clinical features

Age effects on CORE and on endogeneity scores (considered individually and as the sum ENDOG score) were examined, and with quite differing patterns identified for the MEL and NON-MEL groups. First, individual endogeneity scores did not increase with age, either in the assigned MEL or NON-MEL groups (where the mean correlation coefficients were 0·08 and 0·04 respectively). Similarly total ENDOG scores were not associated with age in the MEL or NON-MEL groups (*r*s of 0·06 and 0·10). Secondly, total CORE scores increased with age in the MEL subgroup ($r = 0·31$, $P < 0·01$) but not in the NON-MEL subgroup ($r = 0·03$). In the MEL group, the age association with CORE scale scores was more marked for the agitation scale ($r = 0·42$) than for the non-interactiveness (0·25) and retardation (0·18) scales, while for the NON-MEL group no CORE scale was associated with age (*r*s of $-0·01$ to $+0·03$). In case polarity influenced any age effect, we repeated the correlations in our 39 bipolar melancholic subjects. Here age was weakly associated with total CORE scores ($r = 0·20$) and variably with the three respective CORE scales (*r*s of 0·27, 0·17 and 0·07). Deleting the bipolar subjects from our overall sample had minimal impact on age and CORE scale correlations. However, as there were few bipolar subjects, we cannot exclude the possibility of a differential age effect across bipolar and unipolar subjects.

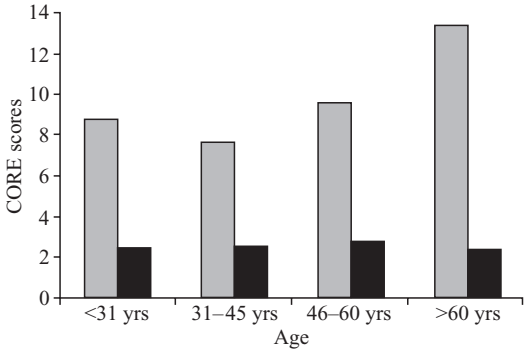

FIG. 1. Comparing CORE scores across age quartiles for melancholic (▒) and non-melancholic depression (■).

Fig. 1 shows CORE scores for MEL and NON-MEL groups assigned across four *a priori* selected age bands. For the NON-MEL subjects the mean CORE scores (proceeding from the youngest to the oldest age group) were 2·4, 2·5, 2·7 and 2·3, with an analysis of variance ($F = 0·17$) confirming no association between CORE scores and age. For the MEL subjects, respective mean scores were 8·8, 7·7, 9·6 and 13·3, with analyses of variance indicating both significant linear ($F = 16·2$, $P < 0·001$) and quadratic ($F = 4·0$, $P < 0·05$) trends, with the 'trend break' to distinctly higher CORE scores being most evident in those MELs aged 60 years or more. Further analyses of the data for the MEL group established that older subjects had more CORE signs rated as 'present' (i.e. 1, 2 or 3) with indicative data being 7·8 for those < 30 years and 11·4 for those aged 60 to 70 years. Secondly, if a CORE sign was rated as 'present', it returned a more severe rating in older subjects (i.e. 1·5 *v.* 1·3 respectively).

Using logistic regression we estimated the probability of each of the CORE signs being present across the age range in both the MEL and NON-MEL groups. For each of the individual CORE items there was little evidence of an age effect in the NON-MEL group (and where the prevalence of most items was very

https://doi.org/10.1017/S0033291701004603 Published online by Cambridge University Press

Table 1. *Probability of a CORE sign being present* (1–3 *v.* 0) *for three specific ages in melancholic subjects only*

CORE item	Age (years)			Item scale*
	30	50	70	
Non-interactiveness	0·40	0·47	0·54	N-I
Facial immobility	0·74	0·80	0·85	Ret
Postural slumping	0·49	0·54	0·59	Ret
Non-reactivity	0·77	0·84	0·89	N-I
Facial apprehension	0·55	0·73	0·86	Ag
Delayed verbal responding	0·33	0·40	0·48	Ret
Shortened verbal responses	0·47	0·53	0·58	N-I
Inattentiveness	0·13	0·22	0·33	N-I
Facial agitation	0·14	0·24	0·38	Ag
Body immobility	0·61	0·67	0·72	Ret
Motor agitation	0·31	0·46	0·62	Ag
Poverty of association	0·52	0·60	0·69	N-I
Slowed movement	0·55	0·62	0·69	Ret
Verbal stereotypy	0·12	0·24	0·43	Ag
Delay in motor activity	0·30	0·41	0·54	Ret
Impaired spontaneity of talk	0·56	0·64	0·72	N-I
Slowing of speech rate	0·32	0·31	0·29	Ret
Stereotyped movements	0·04	0·13	0·32	Ag

* N-I, non-interactiveness scale item; Ret, retardation scale item; Ag, agitation scale item.

low), with the possible exception of slowed movement and verbal stereotypy. By contrast, for the MEL group, there was a general phenomenon for the probabilities for each item to be more likely to be rated as present with age. Table 1 provides representative MEL data in giving prevalence rates for three specific ages. For example, for the item 'facial immobility', its probability of being present in a 30-year-old was 0·74, as against 0·80 in a 50-year-old and 0·85 in a 70-year-old. CORE agitation scale items (e.g. facial agitation, motor agitation, stereotyped movements) showed the most distinct rate rise with age, although they generally had a low base-rate in the youngest represented age group.

Does age influence the capacity of clinical features to predict melancholia?

We undertook a series of discriminant function analyses examining the capacity of two clinical variables (i.e. total ENDOG score and total CORE score) and of age to discriminate those assigned to the MEL and NON-MEL diagnostic groups. The CORE score alone was superior to the ENDOG score alone in assigning subjects to the MEL (67% *v.* 56%) and NON-MEL (97% *v.* 81%) groups, with respective kappas of 0·68 and 0·39.

As noted in the Introduction, our earlier analyses (Parker *et al.* 1995) had suggested that the CORE score largely made any contribution of endogeneity scores redundant in predicting 'melancholia', while the addition of CORE score (after allowing for any effect of endogeneity symptoms) did make an additional prediction. Specifically, the addition of CORE to ENDOG increased the classificatory power (κ increasing from 0·39 to 0·70) whereas the addition of ENDOG to CORE made little improvement (κ increasing from 0·68 to 0·70). Age alone had moderate predictive power $\kappa = 0{\cdot}48$). The addition of age to CORE scores as a predictor had a minimal effect (increasing κ from 0·70 to 0·74), while the addition of age to ENDOG was more distinctive κ increasing from 0·39 to 0·54). The addition of age to ENDOG and CORE increased κ marginally from 0·70 to 0·72. Such results indicate the efficiency of CORE scores alone in distinguishing melancholic from non-melancholic depression, and in addition (the 'sufficiency' component) the minimal additional contribution of endogeneity symptoms once CORE scores have been entered as a predictor. They also reveal that age alone has modest power to predict diagnostic assignment and, when added to ENDOG scores made an additional prediction, but when added to CORE scores did not make an additional prediction – again suggesting a distinct overlap between CORE scores and age, and independence of age scores and ENDOG scores.

DISCUSSION

As reviewed elsewhere (Parker & Hadzi-Pavlovic, 1996), psychomotor disturbance (PMD) has long been held to be a key marker of melancholic depression, with the CORE measure being developed as an operationalized behavioural measure of its key constructs. As a surface (or recordable) marker of presumed pathophysiological processes, PMD potentially allows identification of discrete neurobiological groups. If PMD is specific to and an obligatory feature of melancholic depression, then it has the capacity to act as a highly efficient, diagnostic-specific tool. Encouraged by data supporting that view, we have previously argued for a hierarchical model (Parker, 2000), where the presence of PMD distinguishes melancholic

https://doi.org/10.1017/S0033291701004603 Published online by Cambridge University Press

from non-melancholic depression, while the presence of delusions and/or hallucinations (together with even more severe expressions of PMD) distinguishes psychotic from melancholic depression. As noted, however, we have since suspected that PMD may be less severe in younger melancholic depressive subjects. If true, this raises certain questions as to whether the overall phenotypic pattern (or certain component expressions) of 'melancholia' differs across age groups and, if so, has implications for the pathogenesis, diagnosis and treatment of melancholia.

While we have previously reported analyses involving the refined CORE measure from both contributing samples (Parker *et al*. 1990, 1998), we have never previously aggregated the two databases. Here we further restricted the sample by excluding those with psychotic depression and those not at episode nadir, with the latter strategy designed to test more fairly the utility of current clinical features to diagnostic subtyping. Furthermore, and differing from our previous studies, we sought to improve our criterion clinical definitions of 'melancholic' and 'non-melancholic' subjects by assigning only those who met (or failed to meet) both DSM-III-R and clinical criteria, thus excluding diagnostically problematic subjects from the contrast groups.

Those assigned as melancholic (MEL) were significantly older both at first depressive episode and at MDU assessment, arguing for consideration of both age effects. We also judged it worthwhile to examine any effects of depression 'severity' and recurrence. Severity can be a proxy of depressive subtype, and any age effect might not relate to age *per se* but an age-related variable such as having experienced more frequent episodes.

Our results can be readily summarized. As quantified by the CORE measure, psychomotor disturbance increased with age only in the MEL subjects, and with the quadratic analysis suggesting a trend break for distinctly higher PMD in those MELs over the age of 60 years. Item by item, as well as scale score analyses, suggested that the age effect was a diffuse one impacting on all CORE items, but that age influenced agitation scores more distinctly. By contrast, for our set of 'endogeneity symptoms' (and which are strongly represented in the DSM-III-R and DSM-IV criteria set for melancholia), there was no suggestion of an age effect on their expression.

The intriguing difference between age effects on PMD and endogeneity symptoms deserves intensive study. If observable PMD and endogeneity symptoms are both clinical markers of 'melancholia', why would only one be influenced by age? The answer may be methodological, in that we may have measured one domain more validly than another. It may reflect measurement error, with signs being more easily observed and/or over-rated in older patients. Alternatively, it could be that melancholia is defined to a far greater extent by PMD than by endogeneity symptoms, and that any impact of age on the phenotypic expression of 'melancholia' can therefore only be established for PMD. It could also reflect a direct or indirect effect of the 'ageing brain' on the phenotypic expression of 'melancholia'. Our 'model' for understanding the expression of PMD in melancholia (Austin & Mitchell, 1996) is based on the neural network model of Alexander *et al*. (1986), which supposes that certain neuroanatomical and neurochemical circuits exist, and with those connecting the basal ganglia and pre-frontal cortex being of relevance here. Disruption of specific circuits is held to induce a triad of features (i.e. PMD, depressed mood and cognitive dysfunction). These circuits may be disrupted functionally and/or structurally, allowing two expressions of 'melancholia'. It could be that PMD is more evident and distinct when it has a structural (and not merely a functional) basis and, as this expression is more common in older subjects (with increased likelihood of basal ganglia volume reduction and/or hyperintensities), this could contribute to an age effect as identified in this study. Brodaty (1996) has noted that 'Intuitively, one might expect that age-associated degenerative and vascular brain pathology would be associated with more organic or neurological types of depression', where 'the putative pathogenesis is disruption of ascending aminergic systems', and where both 'depression and ageing combine to increase the risk of … psychomotor change'. Such a hypothesis is clearly capable of testing by structural imaging studies, and such investigations would appear to be of distinct benefit in our understanding of both 'melancholia' and its patho-

https://doi.org/10.1017/S0033291701004603 Published online by Cambridge University Press

genesis, and perhaps advance our capacity to treat such disorders.

In this paper, we once again considered the comparative utility of dimensionally measured endogeneity symptom (ENDOG) and CORE scores to predict allocation to clinically and DSM-diagnosed melancholia, and the capacity of each to be 'sufficient' – in the sense of making the other a redundant predictor. It should be emphasised that such analyses differ from our earlier latent class analyses (Parker *et al.* 1994) where we considered individual endogeneity symptoms and CORE signs as predictors of diagnostic subtype. Here, in effect, we merely examined severity of a representative set of endogeneity symptoms and severity of PMD. As in our previous studies involving three differing samples, we showed some overlap or shared variance between the two measures (Parker *et al.* 1990, 1994, 1999). Before and after entering age as a predictor, the CORE score was superior to the ENDOG score. It was again largely sufficient, in the sense of almost obviating the contribution of the ENDOG score, and dominated the predictive discrimination. While age alone was predictive ($\kappa = 0{\cdot}48$), adding age as a predictor to CORE and ENDOG scores increased prediction marginally (κ increasing from 0·70 to 0·72). Study data indicate an age impact on melancholia but that CORE scores (as rated here) effectively captured that impact. Our predictor analyses are in line with our previous study (Parker *et al.* 1995) and where we established that CORE-measured PMD dominated the comparative prediction of melancholia and with endogeneity symptoms making only a slight additional contribution. Thus, and as considered previously, despite demonstrating an age effect on psychomotor disturbance, we can still model 'melancholia' as a 'core and mantle' disorder, with psychomotor disturbance being its central clinical feature and with there being a narrow mantle of endogeneity symptoms.

If the phenotypic expression of melancholia is influenced by age, then there are likely to be important implications involving its biological determinants and in impacting on the effectiveness of differing antidepressant treatments that have differential actions on aminergic circuits. Any age effect on the phenotypic expression of melancholia thus warrants examination of differential age effects on its treatment by differing narrow-based and broad-based antidepressant treatments.

We thank Kerrie Eyers, Christine Boyd, Heather Brotchie for study assistance, and the NHMRC (Grant 993208) and the NSW Department of Health (Infrastructure Grant) for funding assistance.

REFERENCES

Alexander, G. E., DeLong, M. R. & Strick, P. L. (1986). Parallel organisation of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience* **9**, 357–381.

Austin, M.-P. & Mitchell, P. (1996). Melancholia as a neurological disorder. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 223–236. Cambridge University Press: New York.

Brodaty, H. (1996). Melancholia and the ageing brain. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 237–251. Cambridge University Press: New York.

Hamilton, M. (1967). Development of a rating scale for primary depressive illness. *British Journal of Social and Clinical Psychology* **6**, 278–296.

Parker, G. (2000). Classifying depression: should paradigms lost be regained? *American Journal of Psychiatry* **157**, 1204–1211.

Parker, G. & Hadzi-Pavlovic, D. (1996). Development and structure of the CORE system. In *Melancholia: A Disorder of Movement and Mood* (ed. G. Parker and D. Hadzi-Pavlovic), pp. 82–129. Cambridge University Press: New York.

Parker, G., Hadzi-Pavlovic, D., Boyce, P., Wilhelm, K., Brodaty, H., Mitchell, P., Hickie, I. & Eyers, K. (1990). Classifying depression by mental state signs. *British Journal of Psychiatry* **157**, 55–65.

Parker, G., Hadzi-Pavlovic, D., Wilhelm, K., Hickie, I., Brodaty, H., Boyce, P., Mitchell, P. & Eyers, K. (1994). Defining melancholia: properties of a refined sign-based measure. *British Journal of Psychiatry* **164**, 316–326.

Parker, G., Hadzi-Pavlovic, D., Austin, M-P., Mitchell, P., Wilhelm, K., Hickie, I., Boyce, P. & Eyers, K. (1995). Subtyping depression I: Is psychomotor disturbance necessary and sufficient to define melancholia? *Psychological Medicine* **25**, 814–823.

Parker, G., Hadzi-Pavlovic, D., Roussos, J., Wilhelm, K., Mitchell, P., Austin, M-P., Hickie, I., Gladstone, G. & Eyers, K. (1998). Non-melancholic depression: the contribution of personality, anxiety and life events. *Psychological Medicine* **28**, 1209–1219.

Parker, G., Wilhelm, K., Mitchell, P., Roy, K. & Hadzi-Pavlovic, D. (1999). Sub-typing depression: testing algorithms and identification of a tiered model. *Journal of Nervous and Mental Disease* **187**, 610–617.